Control of Enuresis with Imipramine

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One child in five wets the bed at the age of 4 (Bransby, Blomfield, and Douglas, 1955). Thereafter the incidence falls, but even at the age of 14 between 2 and 3% of the population remain enuretic. Many pharmacological remedies have been applied to this problem in the past, but there have been few controlled trials, and little evidence of better than placebo response with such traditional remedies as amphetamine and belladonna derivatives (Kim, 1959; Glicklich, 1951).

Until the introduction of the newer antidepressant drugs, the only effective treatment has been the alarm (Mower and Mower, 1938; Lovibond, 1964). The acceptability of this form of treatment may be limited by socio-economic factors and the high degree of co-operation demanded from both child and parent. The relapse rate with the alarm is high (Turner and Young, 1966). A safe and effective pharmacological method of control or cure remains a desirable goal.

MacLean (1960) was the first to report the apparent effectiveness of imipramine in nocturnal enuresis, and his initial uncontrolled observations preceded more than 60 subsequent papers on the subject. In this welter of literature we have noted only 12 satisfactorily designed trials. However, only 2 of these (Poussaint and Ditman, 1965; Friday and Feldman, 1966) were conducted on children referred to a paediatric out-patient clinic, the remainder having been carried out on children in institutions, service recruits, or disturbed children being seen at a psychiatric centre.

Friday and Feldman (1966) studied 51 children, the majority of whom came from a socially deprived background, with a high incidence of neurotic behaviour. These were given a brief course of treatment with 10 or 25 mg. imipramine, depending on age; 82% of the children had their wetting frequency reduced by over 50% while on the drug, as compared to 45% of those children receiving placebo.

Poussaint and Ditman (1965) reported on 47 enuretics in a double-blind placebo controlled trial with cross-over: high frequency enuretics were studied while receiving 25 or 50 mg. imipramine according to age. No assessment of wetting frequency was made during a preparatory control period, and the children did not attend the clinic during the treatment period. They found imipramine much superior to placebo. Treatment was continued after the trial period, and 24% of their subjects were ultimately cured after gradual withdrawal of the drug.

The period of observation after stopping treatment extended to 3 months. It was suggested that the response was dose dependant, and that gradual withdrawal led to a better result than sudden withdrawal. No description of incidence of emotional disturbance or of family history was given for their population.

Our study has been designed to test whether or not these authors' findings could be repeated in a population fairly typical of that seen in an English Local Authority enuretic clinic.

We have, in addition, extended the period of follow-up study, and have included in the design of our trial a no-treatment control period.

Observations have been made on the physical environments and psychiatric status of the patients and their relatives.

Material and Method

The subjects were taken from children referred to a Local Authority enuretic clinic which is run in the paediatric department of University College Hospital. Any child of school age with a history of nocturnal enuresis more than twice a week was provisionally accepted for the trial.

At the first attendance a detailed history of the enuresis, general health, development, and behaviour of the child was taken. A social worker inquired into the social circumstances of the family, and if necessary made inquiries from other social agencies.

A physical examination was made, and samples of blood and urine taken for analysis. Each child was asked
to keep a record of the bed-wetting, and this was discussed at the second visit, a fortnight later, when a second sample of urine was collected and other investigations arranged if indicated. Thereafter each child attended the clinic at fortnightly intervals. At the third visit, if investigations revealed no disease or abnormality of the urinary tract, and record keeping confirmed that the bed was wet three or more times in a fortnight, the child was admitted to the trial. It is interesting to note that of 75 patients for whom the pre-trial month records were completed, only 5 had more wet nights, and 10 the same, as the mother reported. The remainder all 'improved' substantially, by an over-all average of 5-4 dry nights/month. Those reported as having between 4 and 8 dry nights improved the most, by up to 18 nights.

If treatment was needed it was then explained that the child would be receiving tablets which would vary in content (and would sometimes be inactive) according to a predetermined schedule, in order that the effect of the drug might be studied.

In all, 81 consecutive referrals were considered for the trial, of whom 33 were referred by school medical officers, 31 by general practitioners, and 17 from other clinics in the hospital. There was no significant difference between these three groups in age, sex, or emotional disturbance (Table I). 30 had previously been dry for at least a month. The remainder had no dry periods for more than a few days.

Physical examination showed no relevant abnormality, though there were various incidental findings, e.g. squints, obesity, and non-significant cardiac murmurs. Urinary symptoms other than enuresis were present in 10 children, but none of these had any significant abnormality on examination of the urine. Urine examination was abnormal in 21 children (Table II).

Four children had significant bacilluria. None of these had albuminuria, but 3 had pyuria. Cell counts in the other were normal. 2 had an abnormal intravenous pyelogram, and one, the only boy of the 4, had unilateral pelvi-ureteric obstruction with hydronephrosis.

There was no increased frequency of daytime wetting or secondary enuresis amongst the 22 with any abnormality of the urine. The trend, though not statistically significant, is for there to be fewer urine abnormalities amongst the secondary enuretics.

We considered 26 of the children to be psychologically disturbed. Among these were 14 whose parents had expressed concern at their child's behaviour, and a further 12 whose parents had made no complaint.

There were no mentally handicapped children, and none in institutional care.

School reports were obtained whenever possible, and of the 70 for whom we had information, 24 were thought by their teacher to be working below their full potential, and 17 were considered to be disturbed in behaviour. The teachers' assessment of disturbance agreed more closely with ours than with the parents' assessment.

The occupations of the fathers were mixed, though, as can be seen from Table III, there was a preponderance of manual workers, especially the semiskilled and unskilled.

Of the mothers, 18 worked full time, 28 worked part time, and 4 took work in at home. Housing conditions were often unsatisfactory, but 54 of the children had a bedroom to themselves or shared with one other child. Only 14 families were in very crowded conditions (persons per room more than 1:5), or condemned buildings. On the other hand, 22 shared a lavatory with another family, or had to use one outside or more than one floor away. 7 children shared a bed with a sib.

The parents were often on bad terms, and in 19 families, there was open disharmony or the parents
were apart. 17 parents had either suffered from overt psychiatric illness or were considered to show it when seen at the clinic.

A family history of enuresis was obtained in 51 cases (Table IV).

The type and degree of enuresis are often considered to be relevant to prognosis. 29 children were still wet by day occasionally. Daytime wetting was, as might be expected, most frequent under the age of 8 (18 cases), and girls were more often affected than boys (16 cases). 30 were said to have had a month or more of consecutive wet nights, and in the month before attending only 7 were said to have had more than 14 dry nights.

Eleven children had associated faecal soiling, defined as significant soiling of the pants with faecal material more than once in the last year.

Though none of these factors necessarily had any bearing on the aetiology of the enuresis, they clearly are relevant to any appraisal of the results of the treatment.

**Trial Procedure**

Dosage was calculated on the basis of surface area, using the percentage method (Butler and Richie, 1960) (Table V).

Two dosage schedules were used, based on maximum doses of 75 mg. (high) and 50 mg. (low), respectively. Active drug and a placebo were used in a double cross-over design with 9 treatment groups, and each strength or placebo was dispensed in uniform packs of 16 white tablets. (This ensured that tablets were returned, as an extra check on consumption.)

**TABLE V**

<table>
<thead>
<tr>
<th>Surface Area (m²)</th>
<th>Low Dose (mg.)</th>
<th>High Dose (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0·55 - 0·62</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>0·63 - 0·76</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>0·77 - 0·92</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>0·93 - 1·10</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>1·11 - 1·28</td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>1·29 - 1·44</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>1·45 - 1·61</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>1·62 +</td>
<td>50</td>
<td>75</td>
</tr>
</tbody>
</table>

In practice, use of the lower range usually means giving a dose of 25 mg. between the ages of 4 and 7, 35 mg. between 8 and 11, and 50 mg. over 11.

Patients were allocated by a stratified randomization consisting of sets of Latin squares, catering for age, sex, and previous psychiatric treatment, which in the absence of any better criterion was used as an operational definition of emotional disturbance. This randomization was superimposed on the 9 treatment combinations to ensure, so far as possible, that there was an even distribution of treatments within each group of children of similar age, sex, and psychiatric status.

The allocation to treatment group was not known by any of the clinic staff seeing the child.

At the end of the third month of treatment, each treatment was split in two. Half the patients stopped treatment abruptly, the rest having a gradually reduced dosage over a four-week period. This was also done according to a pre-arranged random plan. After the drug was stopped each child was asked to keep a record for a further month, and during this time no further treatment was given. At the end of this month further treatment, either by drugs or by the alarm as indicated, was given if necessary, but this did not count as part of the trial.

**Results**

Of 81 subjects who were considered for the trial, 14 were excluded because of urinary infection or improvement before treatment and 5 others stopped attending before treatment was started. Of the 62 who entered the trial, 3 gave no results, 1 being too unreliable in taking tablets and reporting, and 2 lapsing soon after the start of treatment. This left 59 subjects for analysis. Of the other 3 who entered the trial, 1 started on a high dose and 2 on placebo.

The figures analysed consisted of a score, representing the number of dry nights out of 28, for each of 4 periods: Period 1, before treatment; Period 2, first treatment; Period 3, second treatment; Period 4, third treatment (usually first treatment repeated).

In some cases the number of nights observed within a period was less than, or more than, 28. In such cases the score was calculated as the number of dry nights multiplied by 28 and divided by the number of nights observed.

**Within subjects analysis, imipramine versus placebo.** 17 subjects had a treatment scheme in Periods 2, 3, and 4 following one of the 3 patterns: Placebo, Low, Placebo; Placebo, High, Placebo; Low, Placebo, Low.

If the drug has a useful effect, we should expect Period 3 to show a higher score than either Period 2 or Period 4 in either of the first two patterns; Period
3 to show a lower score than either Period 2 or Period 4 in either of the last two.

Of the 17 subjects, 15 did in fact show this result, the score either going up and then down again for Placebo, Drug, Placebo or going down and then up again for Drug, Placebo, Drug. Of the other 2 subjects, one showed no effect at all, the score remaining constant for all three periods, while the other showed the reverse of the expected effect, going up and then down again for Drug, Placebo, Drug.

The result is so clear cut that a test of significance is unnecessary. If a probability is required, it may be noted that if the drug had no effect, then we should expect half the results to favour the drug, and half to favour the placebo in the long run (ignoring results that show no difference). In this case, the probability of 15 results going one way and only one the other is $0.0005$ or 1 chance in 2000. There can, therefore, be little doubt that imipramine has a genuine effect.

**TABLE VI**

*Within Subject Analysis: High Dose Versus Low Dose*

<table>
<thead>
<tr>
<th>Result</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$++$</td>
<td>2</td>
</tr>
<tr>
<td>$+$</td>
<td>3</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>$-$</td>
<td>3</td>
</tr>
<tr>
<td>$--$</td>
<td>2</td>
</tr>
</tbody>
</table>

Within subjects analysis, high dose versus low dose. 11 subjects had one of the patterns: High, Low, High; or Low, High, Low.

We can classify the results for each subject on a five-point scale as follows. If the score goes up and then down again, or down and then up again, classify as $++$ if the high dose results are better than low dose, or $--$ otherwise. For any other pattern, classify as $+$ if the average score on high dose is better than the average on low dose, classify as 0 if the averages are equal, classify as $-$ otherwise.

The results are shown in Table VI and are seen to be completely symmetrical. There is no evidence whatever, from this analysis, that the high dose is more effective than the low.

Between subjects analysis. In the between subjects analysis, an approximation to Wilcoxon's test (Wilcoxon, 1945) was used for calculating probabilities, two-tailed probabilities being used in all cases. This approximation is based upon finding Kendall's statistic (Kendall, 1962), with its expectation and standard error, allowance being made for tied values.

The first test was of the Period 1 (before treatment) scores, classifying according to the first treatment (to be used in Period 2). This is a test of the adequacy of randomization in equalling the groups. Table VII shows the results to be satisfactory in this respect.

In each of Periods 2, 3, and 4 the distributions of the scores have been tested according to the treatment in use during that period. The results are set out in Table VIII.

Only Period 4 shows any statistically significant differences here, both doses doing better than placebo. In Periods 2 and 3 also the differences are in the expected direction (though Table VIII does not show this). There is no significant difference between high and low doses.

For Period 2, what difference there is, is in the direction of high doing better than low, but in Period 3 the sign of the difference is reversed. In Period 4 the observed difference is so small that chance alone would usually produce a greater discrepancy.

A further analysis to test the effect of different doses can be made by comparing the differences between Period 1 and Periods 2, 3, and 4. This gets rid of some of the differences between subjects and thus makes the test more sensitive. When this is done there is still no significant difference between the effects of high and low doses. Because it seemed possible that initial age and sex differences

**TABLE VII**

*Comparison in Pretreatment Period*

<table>
<thead>
<tr>
<th>First Treatments To Be Used</th>
<th>Two-tailed Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo versus Low</td>
<td>0.23</td>
</tr>
<tr>
<td>Placebo versus High</td>
<td>0.90</td>
</tr>
<tr>
<td>Low versus High</td>
<td>0.42</td>
</tr>
</tbody>
</table>

**TABLE VIII**

*Comparison in Three Treatment Periods*

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Two-tailed Probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 2</td>
</tr>
<tr>
<td>Placebo versus Low</td>
<td>0.52</td>
</tr>
<tr>
<td>Placebo versus High</td>
<td>0.36</td>
</tr>
<tr>
<td>Low versus High</td>
<td>0.33</td>
</tr>
</tbody>
</table>
between the groups were affecting the comparison between high and low doses, different age and sex groups were analysed separately. The results do not suggest that these differences between the groups could be responsible for the lack of significant differences.

**Long-term effect.** There were 12 patients who had placebo in both Periods 2 and 4. Long-term effects can be sought by comparing the Period 4 results with the Period 2 results, dividing into groups by the Period 3 treatment. The results in Table IX show no sign of any effect of the drug being carried over from Period 3 to Period 4.

An exact Wilcoxon test was used for these probabilities as the numbers of observations are small.

An interim analysis, 9 months after the start of the trial, revealed a significant drug effect. On the basis of this finding, we decided it was unethical to continue to use placebo, or to allow patients who had only been given placebo to go through a further month without effective treatment.

Because of these and other losses only 32 patients were observed for a month without any treatment after Period 4.

The results of this group showed no significant differences between the scores of those suddenly withdrawn from the drug, and those gradually withdrawn. The design of the trial made it possible for patients to have had continuous treatment for from 4 to 16 weeks. The length of continuous treatment before withdrawal made no significant difference to the score.

On the other hand there was a significant relation between the total quantity of drug received, and improved scores after withdrawal (p = 0·03).

**Side-effects.** Before starting the trial, parents were warned that their children might experience such minor effects as constipation, and dry mouth. In fact only 5 patients reported these side-effects, and 3 of them were receiving placebo at the time that the symptom was complained of.

The most important side-effect, which was reported in 3 patients in the population under study, but which has been seen in a further 3 patients in this clinic, was an alteration in mental state. The child became restless and irritable, fearful and fidgety, found it difficult to concentrate, and did worse at school. There was also a disturbance in sleep, with nightmares, restlessness at night, and difficulty in going to sleep. Sleep disturbances without more widespread behaviour disturbances were reported in a further 3 patients.

| TABLE IX  
Comparison of Periods 2 and 4, when Placebo was used in both |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 3 Treatments</td>
<td>Two-tailed Probability</td>
</tr>
<tr>
<td>Placebo versus Low</td>
<td>0·71</td>
</tr>
<tr>
<td>Placebo versus High</td>
<td>0·89</td>
</tr>
<tr>
<td>Low versus High</td>
<td>0·29</td>
</tr>
</tbody>
</table>

It was noted that the patients who showed this behaviour disorder were all thought to be disturbed before treatment, and the change seems to represent an exacerbation of their normal behaviour.

One child, not in the trial, developed acute peptic ulceration 3 weeks after the drug was stopped, but this is probably coincidental. No similar incidents have been reported to the Dunlop Committee. This child was in peculiarly adverse home circumstances, and the relief of his enuresis did nothing to improve these.

**Follow-up studies.** Of the 59 who entered the trial, follow-up data were obtained from 52, usually during continued attendance, but in a few cases by correspondence. Follow-up ranged from 3 to 14 months, and 36 children were followed for over 6 months.

The disposal of patients at the time of writing is given in Table X.

Active social work (home visits, help with housing problems, and liaison with other social agencies) was carried out with 18 families. 8 parents were thought to need treatment for their mental state, and this was arranged through the general practitioner, or the hospital psychiatric department.

Treatment at the end of the double-blind trial was decided upon by the use of simple clinical criteria. When a patient had responded to imipramine during the double-blind period this drug was given another try. When the patient had only received placebo a trial of imipramine also was used.

The children who had only received imipramine in the low dose range were usually given a larger

| TABLE X  
Disposal |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Referred to other clinics</td>
<td>6</td>
</tr>
<tr>
<td>Discharged</td>
<td>32</td>
</tr>
<tr>
<td>Lapsed</td>
<td>26</td>
</tr>
<tr>
<td>Continues to attend</td>
<td>17</td>
</tr>
</tbody>
</table>
dose (corresponding to the high dose range). When imipramine had failed to produce any beneficial effect, or when the child relapsed despite a prolonged or repeated course, the alarm was used. Where this was not practicable for social or other reasons a trial was usually given with either amitriptyline or dexamphetamine.

At some stage during their attendance at the clinic 56 patients were given imipramine. Of these, 48 improved, 5 were unchanged, and 3 wet more frequently while taking the drug. Amongst the 56 who at some time took imipramine, 20 became dry while on the drug for 14 or more consecutive nights. But of this subgroup only 3 were known to have remained dry after the drug was withdrawn. At the time of writing, 2 of these remain dry, without any treatment at all, for 6 and 11 weeks. One other child relapsed 9 weeks after the drug was withdrawn. There was one other child who had been dry for more than 14 days while on the drug, but he stopped attending when the drug was withdrawn. More responders were children under $9 (X^2$ with Yates’ correction $= 6.59, p = 0.0015$), and ‘secondary’ enuretics ($X^2 = 4.489, p = 0.017$).

**Table XI**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Record Keeping</th>
<th>Imipramine</th>
<th>Bell and Pad</th>
<th>Amitriptyline</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. given treatment</td>
<td>81</td>
<td>56</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured for at least 1 month when treatment withdrawn</td>
<td>10</td>
<td>3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Continues to attend and still on treatment</td>
<td>0</td>
<td>8</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Further courses of imipramine did not improve the cure rate, and in fact the response was not as good in many subjects. The outcome for each treatment is shown in Table XI.

All treatments used produced some improvement, if they did not cure, in nearly all the children who had them.

The degree of improvement was greatest for those who had the alarm, and least for drug treatment. A detailed appraisal of improvement is difficult to make, since equal increments in dry nights from different baseline wetting rates cannot be regarded as equivalent, nor can percentage changes. A further complication is the extreme variability in wetting that many children show from week to week. This made it particularly difficult to decide how long it would be reasonable to continue treatment with imipramine in the hope of a response. 15 children who had the drug showed consistent wetting scores per week in the control period. 11 improved within a fortnight, but the remainder took 4, 4, 5, and 7 weeks, respectively, to show a response. No child who improved after more than a fortnight became consistently dry on the drug.

**Discussion**

Our results confirm those of other workers in showing that imipramine is a drug which reduces enuresis in the majority of children. Including the results of treatment after the trial, the improvement amounted to consistent dryness for a fortnight or more in 20 of the 56 who had imipramine, but in only 2 has this happy state persisted. This finding contrasts with that of Poussaint and Ditman who state that a 3-month course had been established in 24% of their cases. We could not confirm their finding that sudden withdrawal was related to relapse. Whatever the mode of withdrawal, 53 of our patients relapsed within a week, though after treatment they did not wet so often as before. Relapse after withdrawal did not appear to be a rebound phenomenon, as there was little difference between the wetting scores of the first and fourth weeks after withdrawal.

It has also been claimed that increasing the dose of imipramine leads to improved results. The trials for which this claim has been made have all given uniform doses for children between the ages of 5 and 12. This ignores one of the basic principles of paediatric prescribing, i.e. that dosage should be related to the surface area of the child. In adopting this procedure we found no differences between giving a dose related to a basic adult dose of 50 or 75 mg.

The difference between our results and those of Poussaint and others cannot be explained by our longer follow-up, since relapse occurred so soon after withdrawal.

A number of our patients received intermittent therapy in the post-trial period, following the suggestion of Epstein and Guilfoyle (1965), and it may be that this was inimical to long-term success. There was no evidence to suggest that these patients did worse than those who had had the drug for long periods, though the numbers are small. Nor did continuous treatment, after control with the drug was achieved, appear to improve outcome.
Control of Enuresis with Imipramine

Poussaint and Ditman do not appear to have used a control period. We found that the majority of patients had fewer wet nights during the month of record keeping alone than the parent reported, and that some improved to the point where no further treatment was needed. This finding casts doubt on any trial which uses the reported number of dry nights as a baseline. Whether this represents genuine improvement or misreporting by the parent is uncertain.

There were 3 girls and 1 boy in the sample who had urinary infections, a higher incidence than would be expected from the population at large (Kunin, Zacha, and Paquin, 1962). None of these complained of specific urinary symptoms; all had complained of abdominal pain, but so had many other non-infected children. None had albuminuria, though many patients who had transitory albuminuria had no urinary infection. Routine urine microscopic and bacteriological screening for all patients presenting with enuresis is important.

Routine testing for albuminuria does not seem to be of any value. It also appears from our findings that diurnal incontinence, which paediatricians commonly believe to merit particular investigation, is not necessarily associated with urinary tract abnormality or infection, and does not by itself justify full uroradiological screening.

Of 67 who accepted treatment in this series, 21 recovered; 17 more are still attending. The proportion who stopped attending while having drug treatment is only 13.5%, and compares favourably with the lapse rate for the alarm of 29.5% (Young and Turner, 1965), especially in the context of a clinical trial. Few of the factors we studied appear to be relevant to either ultimate success or response to imipramine.

An effective pharmacological cure remains as desirable as ever. Unfortunately we were not able to demonstrate that imipramine has this effect. It is, however, clearly useful when temporary control is required for holidays or other times of need, or when circumstances do not permit the use of the alarm. Though no adverse effects of long-term administration have been reported, we have preferred to be cautious in prescribing imipramine for the control of enuresis for more than a few months.

Summary

A double-blind double cross-over trial of imipramine at two dosage levels, and a placebo, for the treatment of nocturnal enuresis is described. The subjects were 62 schoolchildren attending an outpatient clinic. Dosage levels were related to size, based on surface area, equivalent to single adult doses of 50 and 75 mg.

Imipramine proved much more effective than placebo in reducing enuresis in many children. The higher dosage level was no more effective than the lower level. Relapse of enuresis often stopping treatment was frequent. Different techniques of administration and withdrawal made no difference to outcome.

We are grateful to Dr. L. B. Strang and to the late Dr. S. Yudkin for the help and advice they have given us, and for allowing us to make use of the facilities of the Children’s Welfare Department at University College Hospital; to Professor D. R. Laurence for much helpful advice and criticism; to Dr. W. G. Harding, Medical Officer of Health for Camden, for his encouragement and help in obtaining subjects for the trial, and to all his colleagues and the general practitioners in the Borough who referred their patients. Miss H. Mayer and Miss U. Ranji gave invaluable help in the running of the clinic, and in the social investigations.

This trial could not have been conducted without the generous help of Geigy (U.K.) Ltd., and in particular of Dr. Cyril Maxwell.

References